IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA

ALLERGAN, INC. and DUKE UNIVERSITY, Plaintiffs, v. APOTEX, INC. and APOTEX CORP., Defendants.	)	1:10-CV-681
ALLERGAN, INC. and DUKE UNIVERSITY, Plaintiffs, v. SANDOZ, INC., Defendant.	)	1:11-CV-298
ALLERGAN, INC. and DUKE UNIVERSITY, Plaintiffs, v. HI-TECH PHARMACAL CO., INC., Defendant.	)	1:11-CV-650

MEMORANDUM OPINION AND ORDER

Catherine C. Eagles, District Judge.

These consolidated Hatch-Waxman[1] cases concern two patents covering Latisse®, a drug for treating hypotrichosis of the eyelashes. Latisse® is protected by U.S. Patent No. 7,388,029

[1] The Hatch-Waxman Act is the name commonly used to refer to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. §§ 355, 360cc (2012), 35 U.S.C. §§ 156, 271, 282 (2012)).

("the '029 Patent"), which is owned by Duke University ("Duke") and licensed to plaintiff Allergan, Inc. ("Allergan") (collectively "Plaintiffs"), and U.S. Patent No. 7,351,404 ("the '404 Patent"), which is owned by Allergan. Allergan holds the New Drug Application ("NDA") for Latisse®, which has been approved by the Food and Drug Administration ("FDA"). The defendants, Apotex, Inc., Apotex Corp., Sandoz, Inc., and Hi-Tech Pharmacal Co., Inc. (collectively "Defendants") sought to make and sell generic versions of Latisse® without going through the clinical trial process by filing Abbreviated New Drug Applications ("ANDAs") with the FDA, as allowed by the Hatch-Waxman Act, 21 U.S.C. § 355(j).

After receiving notice of Defendants' Paragraph IV certifications,[2] Plaintiffs initiated this lawsuit pursuant to 35 U.S.C. § 271(e)(2)(A), alleging that Defendants infringed their patents. (Doc. 1 at 1[3]; No. 1:11-cv-298 Doc. 1 at 1; No. 1:11-cv-650 Doc. 1 at 1.) Defendants countersued, seeking declaratory judgments that their products do not infringe on Plaintiffs' patents, and that if they do, the patents are invalid due to anticipation, obviousness, inadequate description, and lack of enablement. (Doc. 24 at 15-18; No. 1:11-cv-298 Doc. 22 at 24-26; No. 1:11-cv-650 Doc. 25 at 14-16.) The cases were consolidated. (Doc. 41, 61.)

A bench trial was held in November 2012. Having considered the documentary evidence and testimony, the Court finds that the Plaintiffs have proven infringement and that the Defendants have not proven their defenses. The Court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

[2] See *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1319 (Fed. Cir. 2012), for a discussion of the "Paragraph IV" process.

[3] Unless otherwise indicated, citations to the docket refer to lead case number 1:10-cv-681.

I. Background

Scientists have been researching hair growth agents for decades with little success, and the field of hair growth biology is unpredictable. (Tr. 11/19/12 at 91:10-14.) Latisse® is the only product ever approved by the FDA to stimulate natural eyelash growth. (Tr. 11/19/12 at 83:16-24.) Before Latisse®, the FDA had approved only two hair growth agents; each was for the growth of scalp hair, not eyelashes. (*Id.*)

The effective ingredient in Latisse® is bimatoprost ophthalmic solution. Bimatoprost is a synthetic prostaglandin F ("$PGF_{2\alpha}$") analog and has been termed a "prostamide" by Allergan scientists. (Tr. 11/5/12 at 132:1-6; Tr. 11/6/12 at 149:11-15; Tr. 11/20/12 at 6:20-7:5; *see also* DTX 695 at -028.) Prostaglandins are naturally occurring molecules that play an important signaling role in human biology by binding to cell receptors. (Tr. 11/5/12 at 143:12-146:13.) A receptor is a target protein for a drug molecule that creates a signal to the cell to change its properties and functions. (*Id.* at 143:17-144:14; Tr. 11/6/12 at 175:25-177:15.) Studying receptors is central to pharmacology—the science of drug therapeutics—because knowing what receptors are associated with a biological effect aids in designing a drug to target those receptors and produce or inhibit that effect. (Tr. 11/5/12 at 144:15-18.) Prostaglandins bind with several receptors in the human body; for example, the naturally-occurring $PGF_{2\alpha}$ binds to the prostaglandin F receptor (also called the FP receptor). (*Id.* at 152:18-153:9.) Compounds that bind with more than one receptor are "nonselective"; selective compounds are generally preferable for reducing side effects. (Tr. 11/6/12 at 174:18-25, 175:10-13, 176:20-177:15.)

Bimatoprost was identified in the early 1990s by Dr. Mitchell deLong, a scientist at Proctor & Gamble, during extensive research on prostaglandins in connection with efforts to develop drugs to treat osteoporosis. (*Id.* at 170:13-20, 201:23-202:14.) It was one of many FP-

selective prostaglandins observed to cause hair growth in mice after injections. (*Id.* at 192:4-193:10.) As a result of their research, Dr. deLong and other scientists applied for the '029 Patent on March 31, 2000, and the patent issued on June 17, 2008. (PTX 2 at -130, -136.) At issue in the '029 Patent are claims 1, 8, 14, 18, and 20, which, in short, claim a method of treating hair loss by repeatedly administering to a mammal certain compounds systemically or topically. (*See* PTX 2 at 60:39-61:48, 61:62-64, 62:47-49, 63:4-64:14, 64:19-66:15.)

Scientists at Allergan were also studying bimatoprost in the 1990s, but for the purpose of developing a new glaucoma treatment. (Tr. 11/5/12 at 151:4-13, 201:23-25.) Prostaglandins had been known to treat glaucoma by lowering intraocular pressure ("IOP") since the mid-1980s. (*Id.* at 151:14-152:4.) The FDA approved latanoprost, another $PGF_{2\alpha}$ analog, to treat glaucoma in 1996. (*Id.* at 132:7-10; 191:5-13.) In 2001, the FDA approved bimatoprost for the treatment of glaucoma, (*Id.* at 190:23-191:13; Doc. 155 at ¶ 27); Allergan sells it under the name Lumigan®. (*Id.* at 190:23-191:13.)

Allergan's work on prostaglandins was overseen by Dr. David Woodward. (Tr. 11/5/12 at 151:4-8.) During the clinical trials studying bimatoprost in eyedrop form as a treatment for glaucoma, Dr. Woodward and Dr. Amanda VanDenburgh, who planned and oversaw the clinical trials at Allergan, observed a significant number of reports of the adverse effect of eyelash growth. (PTX 171; PTX 184A; PTX 185A; Tr. 11/5/12 at 210:15-24, 212:5-213:10; Tr. 11/6/12 at 117:23-121:25.) Drs. Woodward and VanDenburgh applied for the '404 Patent on February 4, 2002, and the patent issued on April 1, 2008. (PTX 5 at -631-32.) At issue in the '404 Patent is claim 14, which essentially claims a method of stimulating eyelash growth by applying an effective amount of bimatoprost. (*See* PTX 5 at 13:66-14:45, 18:6-9.)

II. Infringement

In a Hatch-Waxman case, the filing of an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement "if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of [the] drug . . . before the expiration of such patent." 35 U.S.C. § 271(e)(2). The infringement analysis in a Hatch-Waxman case is the same as in any other infringement suit, except that it looks to the future. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997). The patentee seeking relief under § 271(e)(2) thus has the burden to prove by a preponderance of the evidence that the product to be sold following FDA approval will infringe. *Id.* at 1568. Because the purpose of the submission of an ANDA is to obtain approval to market and sell a well-defined compound, "the ultimate question of infringement is usually straightforward" when the generic manufacturer seeks approval to sell the product for the same use as that which is patented. *Id.* at 1569.

Plaintiffs contend that the sale of Defendants' proposed products will indirectly infringe their patents under the doctrines of induced and contributory infringement. *See Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1331 (Fed. Cir. 2003) (holding that indirect infringement actions may be brought pursuant to 35 U.S.C. § 271(e)(2)). The Court finds by a preponderance of the evidence that the sale and marketing of Defendants' generic versions of Latisse® will constitute induced and contributory infringement.

A. Induced Infringement

To show induced infringement, Plaintiffs must prove that Defendants: a) will knowingly induce infringement, and b) possess specific intent to encourage another's infringement. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010); *see* 35 U.S.C. § 271(b).

Circumstantial evidence, such as including "instructions in [a] proposed label that will cause at least some users to infringe the asserted method claims," can prove specific intent. *Id.* at 1060.

The '029 Patent claims a method of treating hair loss by administering to a mammal a compound, the formula for which includes bimatoprost. (PTX 2 at 60:40-41, 63:4-5, 64:18-19; Tr. 11/7/12 at 172-73.) Defendants concede that their products consist of .03% bimatoprost. (PTX 39 at -118; PTX 46 at -482; PTX 59 at -106; PTX 74 at -689; Tr. 11/7/12 at 140:2-9; Tr. 11/8/12 at 17:1-23.) This Court previously construed "treating hair loss" as "arresting hair loss, reversing hair loss, or both, and promoting hair growth," meaning that the invention may arrest hair loss, reverse hair loss, or promote hair growth in the alternative. (Doc. 88 at 3-4.) Defendants' proposed labels instruct patients to apply their products in order to promote hair growth by increasing lash length, thickness, and darkness. (PTX 35A at -045; PTX 39 at -118; PTX 63 at -385; PTX 72 at -499; Tr. 11/7/12 at 157:18-158:7.)

Defendants contend the '029 Patent claims require the compound to promote growth of hair lost as a result of a disease. Such a requirement is not in the language of the patent, nor did Defendants raise this contention during the claim construction proceedings. Moreover, the evidence does not support Defendants' contentions. While Dr. Rosic testified that "reversing hair loss" and "arresting hair loss" mean stopping disease-induced hair loss and making the hair grow back, (Tr. 11/8/12 at 114: 23-115:8, 122:15-123:2), she also testified that she did not use those terms in her dermatology practice. (*Id.* at 114:25-115:1; 122:18-19.) Moreover, Dr. Rosic did not testify that any of the products at issue failed to promote hair growth. (*See id.* at 152:6-10, 155:4-9; Doc. 88 at 3-4.) Defendants' contention that Plaintiffs failed to show that bimatoprost in its intact form is the active ingredient is a red herring; the '029 Patent claims

require only that bimatoprost be administered to treat hair loss and do not claim the process by which it causes hair growth.

Claim 14 of the '404 Patent claims a method of stimulating eyelash growth in mammals by applying an effective amount of bimatoprost to the skin. (PTX 5 at 13:66-14:45, 18:7-10; Tr. 11/7/12 at 167:15-169:20.) Defendants' ANDA products consist of .03% bimatoprost. (PTX 39 at -118; PTX 46 at -482; PTX 59 at -106; PTX 74 at -689; Tr. 11/7/12 at 140:2-9, 169:19-20.) Defendants' products are indicated to treat hypotrichosis of the eyelashes by stimulating hair growth. (PTX 35A at -045; PTX 63 at -385; PTX 72 at -499.) Their proposed labels instruct users to apply a dose, using the provided applicator, repeatedly to the upper eyelid margin. (PTX 35A at -045; PTX 63 at -385; PTX 72 at -499; *see also* Doc. 88 at 4-6 (construing "an effective amount" as requiring repeated applications).)

Defendants contend that their products do not infringe because they do not increase the number of eyelashes. However, Claim 14 as construed by this Court does not require an increase in the number of eyelashes; stimulating hair growth also includes increasing the length and thickness of hairs. (Doc. 180 at 3.) Defendants also claimed at trial that their identical labels cannot be evidence of specific intent because they were required by the FDA. This argument has been rejected by the Federal Circuit. *AstraZeneca*, 633 F.3d at 1061.

B. Contributory Infringement

To show contributory infringement, Plaintiffs must prove that Defendants will sell or offer to sell a product which is a material part of the patented invention for use in practicing a patented process, that the product has no substantial noninfringing uses, and that Defendants knew of the potential for infringement when they filed their ANDAs. 35 U.S.C. § 271(c); *i4i*

Ltd. P'ship v. Microsoft Corp., 598 F.3d 831, 850-51 (Fed. Cir. 2010), *aff'd*, ___ U.S. ___, 131 S. Ct. 2238 (2011).

Defendants' labels establish that the defendants will offer to sell .03% bimatoprost for use in treating hair loss through repeated application to the upper eyelid margin by way of the provided tool. (PTX 35A at -045; PTX 63 at -385; PTX 72 at -499.) Defendants' products are *the* material part of the patented invention, and they have no substantial noninfringing use. Further, Defendants knew of the potential for infringement of the patents when they filed their ANDAs.

As to the '029 Patent, Defendants argue that Mr. Rhatigan's testimony that some patients are on a maintenance dose of Latisse®, using it less than once daily, (Tr. 11/13/12 at 220:16-24), "forecloses contributory infringement." Presumably, Defendants mean to argue that a maintenance dose is a substantial noninfringing use. However, Mr. Rhatigan is not a prescribing physician; moreover, there was no evidence presented that such an alternative use was "substantial." *See Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009) ("[N]on-infringing uses are substantial when they are not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental."); *see also i4i*, 598 F.3d at 851 (holding that substantiality determination is not based only on frequency of the alternative use, "but also the use's practicality, the invention's intended purpose, and the intended market").

The Defendants' only counterarguments as to the '404 Patent—that Defendants lacked specific intent and that their products do not increase the number of hairs grown—have already been rejected.

III. Validity

Defendants contend that the '029 and '404 Patents are invalid as anticipated and as obvious. Patents are presumed valid, and Defendants bear the burden to prove invalidity by clear and convincing evidence. 35 U.S.C. § 282(a); *Microsoft Corp. v. i4i Ltd. P'ship*, ___ U.S. ___, ___, 131 S. Ct. 2238, 2242 (2011). "[A]lthough the standard of proof does not depart from that of clear and convincing evidence, a party challenging validity shoulders an enhanced burden if the invalidity argument relies on the same prior art considered during examination by the U.S. Patent and Trademark Office." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011).

A. Anticipation

Courts employ a two-step analysis in determining whether patent claims are anticipated by prior art. *In re Montgomery*, 677 F.3d 1375, 1379 (Fed. Cir.), *cert. denied*, 2012 WL 3202990 (U.S. Dec. 10, 2012). The first step involves claim construction, and the second step involves comparing the claims, as construed, to the prior art. *Id.* If the prior art reference discloses every claim limitation in the patent, it is anticipatory and renders the patent invalid. *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1336-37 (Fed. Cir. 2010).

"[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). However, it is not enough that the limitation be possible or likely; it must be a necessary feature or an inevitable result of the prior art. *See Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320 (Fed. Cir. 2004); *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999).

A reference may be inherently anticipatory even if the necessary feature was unknown at the time of the prior invention. *Toro*, 355 F.3d at 1321.

1. The '029 Patent

The '029 Patent teaches a method of treating hair loss by administering to a mammal a topical composition consisting of saturated prostaglandin F analogs. (PTX 2; Tr. 11/6/12 at 203:4-24.) Defendants contend that two documents anticipate the '029 Patent: the Johnstone PCT,[4] (DTX 499), and the '819 Patent.[5] (DTX 717.) Both of these references were before the patent examiner during the reexamination of the '029 Patent. (PTX 8A at -197.)

The Johnstone PCT, like the '029 Patent, teaches the use of prostaglandins as hair growth agents. However, as the patent examiner found during reexamination of the '029 Patent, the Johnstone PCT "lacks motivation to modify the prostaglandins taught therein in order to obtain the presently claimed prostaglandins." (PTX 8A at -197.) This is because the Johnstone PCT teaches a method of stimulating the rate of hair growth by administering a prostaglandin compound with the following alpha chain:

(DTX 499 at -009.) This alpha chain has a cis double bond at C5-C6, meaning that it is unsaturated. (Tr. 11/9/12 at 124:15-24, 135:23-25.) Before Dr. deLong's discovery that saturated prostaglandin F analogs could bind, this double bond was thought vital for FP-receptor binding. (PTX 452 at -639; PTX 479 at -472-74; Tr. 11/19/12 at 156:3-6, 160:16-23.)

[4] International Application Published Under the Patent Cooperation Treaty (PCT) No. WO 98/33497 (published Aug. 6, 1998).

[5] U.S. Patent No. 5,688,819 (filed Nov. 18, 1997).

Defendants contend that the Johnstone PCT teaches modification of the C5-C6 bond to saturate the chain, pointing to one place in the PCT describing the alpha chain as "saturated or unsaturated." (DTX 499 at -014.) The Johnstone PCT, however, does not contain any other language or examples of saturated alpha chains. (*See* DTX 499; Tr. 11/19/12 at 152:6-20.) In fact, the Johnstone PCT's claims cover only compounds with the C5-C6 double bond. (DTX 499 at -0032-35; Tr. 11/19/12 at 151:8-10.) Dr. Sherman admitted that the Johnstone PCT only depicts compounds with unsaturated alpha chains. (Tr. 11/9/12 at 135:15-25.) In this context, the Johnstone PCT does not "clearly and unequivocally disclose" the use of saturated prostaglandin F compounds. *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972); *see also Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). Thus, it does not anticipate the '029 Patent.

The '819 Patent claims the application of an effective amount of compounds, including bimatoprost, to the eye to treat glaucoma. (DTX 717 at 13:15-18:24; Tr. 11/9/12 at 204:14-24; Tr. 11/19/12 at 185:12-14, 186:4-6.) Although Defendants concede that the '819 Patent does not disclose hair growth or the application of bimatoprost to the skin, they argue that it inherently anticipates the '029 Patent. Specifically, they contend that when applied as an eye drop, bimatoprost contacts the skin through excess overflow, tearing, and wiping, naturally causing eyelash growth. Though the evidence presented at trial showed that bimatoprost may—or even is likely to—contact the skin when applied through an eye drop for the treatment of glaucoma, it did not show that bimatoprost *necessarily* contacts the skin. *See Toro*, 355 F.3d at 1320. Dr. Noecker, for example, testified that a properly applied drop is not transferred to the skin. (Tr. 11/13/12 at 129:7-16.)

More importantly, even if bimatoprost administered in eye drops does often contact the skin, the evidence did not show that it necessarily grows eyelashes. Dr. Sherman testified that eyelash growth was inherent in the '819 Patent based on Dr. VanDenburgh's testimony about the results from the Lumigan® clinical trials. (Tr. 11/9/12 at 156:12-157:2.) However, those results do not show that bimatoprost applied through an eye drop necessarily grows eyelashes; they show only that some patients experienced the adverse side of effect of eyelash growth. (PTX 536 at -526-27 (six of forty-three patients experienced lash growth); PTX 540 at -013-14 (two of seventeen patients experienced lash growth); PTX 579 at -404-05 (three of sixteen patients experienced lash growth); Tr. 11/6/12 at 107:13-20, 109:15-24.) The mere fact that bimatoprost, when applied through an eye drop, may contact the skin and cause eyelash growth does not mean that such an effective application is inherent in the '819 Patent. *See Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) ("Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." (internal quotation marks omitted)).

2. The '404 Patent

The '404 Patent claims a method for stimulating eyelash growth in a mammalian species by applying an effective amount of bimatoprost to the skin. (PTX 5 at 13:66-14:45, 18:6-10.) Defendants contend that the following documents anticipate the '404 Patent: the October 23, 2000 Brandt presentation,[6] (DTX 6); the October 23, 2000 Brandt press release,[7] (DTX 710); the

[6] Dr. James Brandt, Phase III, 3-Month Comparison of Timolol with AGN 192024: A New Ocular Hypotensive Lipid™ for Glaucoma Management (Oct. 23, 2000).

[7] Press Release, Business Wire, Phase III Lumigan—AGN 192024—Data Presented At American Academy of Ophthalmology (Oct. 23, 2000).

March 2, 2001 Brandt presentation,[8] (DTX 695); a March 2, 2001 Brandt press release,[9] (DTX 720); the May 2001 Brandt publication,[10] (DTX 735); the June 2001 Brandt publication,[11] (DTX 113), (collectively "the Brandt references"); the '029 Patent, (PTX 2); and the '819 Patent, (DTX 717). The '819 Patent and the '029 Patent application were before the patent examiner during the reexamination of the '404 Patent. (PTX 19 at -973-74.)

The Brandt references cannot anticipate the '404 Patent as they were not published before the invention date of the '404 Patent and do not qualify as prior art under 35 U.S.C. § 102(a). *See Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996) ("[A] document is prior art only when published before the invention date."). "[T]he person who first conceives, and, in a mental sense, first invents may date his patentable invention back to the time of its conception." *Id.* at 1577 (internal quotation marks and alterations omitted). Where a party seeks to show conception through oral testimony of an inventor, corroboration is required. *Price v. Symsek*, 988 F.2d 1187, 1194 (Fed. Cir. 1993). A "rule of reason" approach applies to corroboration such that "[a]n evaluation of *all* pertinent evidence must be made so that a sound determination of the credibility of the inventor's story may be reached." *Id.* at 1195. Corroborating evidence may consist of documentary evidence made contemporaneously with the inventive process, oral testimony of someone other than the inventor, or circumstantial evidence about the inventive

[8] Dr. James Brandt, Phase III, 6-Month Comparison of Timolol with LUMIGAN™: A New Prostamide for Glaucoma Management (Mar. 2, 2001).

[9] Press Release, Business Wire, Lumigan 6-Month Phase III Data Presented at American Glaucoma Society Meeting (Mar. 2, 2001).

[10] Dr. Mark Sherwood & Dr. James Brandt, *Six-Month Comparison of Bimatoprost Once-Daily and Twice-Daily with Timolol Twice-Daily in Patients with Elevated Intraocular Pressure*, 45-4 Survey of Ophthalmology S361 (2001).

[11] Dr. James D. Brandt, Dr. Amanda M. VanDenburgh, Kuankuan Chen, & Dr. Scott M. Whitcup, *Comparison of Once- or Twice-daily Bimatoprost with Twice-daily Timolol in Patients with Elevated IOP*, 108(6) Ophthalmology 1023 (2001).

process. *Sandt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1350-51 (Fed. Cir. 2001).

Although the effective filing date of the '404 Patent was not until February 4, 2002, Dr. Woodward and Dr. VanDenburgh are entitled to a conception date in mid-2000. Dr. Woodward credibly testified that he reached "a concrete conclusion that there was a reasonable possibility that local application of bimatoprost would grow hair" in the first half of 2000. (Tr. 11/5/12 at 220:15-20.) Dr. VanDenburgh credibly testified that she and her Allergan colleagues spoke with patent attorneys about filing a patent for bimatoprost as a hair growth agent sometime between the filing of the Lumigan® NDA in September 2000 and the drug's approval in March 2001. (Tr. 11/6/12 at 135:25-136:11.) The corroborating evidence supports a conception date of July 2000 at the latest. The first internal Allergan memorandum summarizing the Lumigan® clinical trial's key findings and indicating that Lumigan® had the adverse effect of hair growth was dated December 29, 1999. (PTX 173; Tr. 11/6/12 at 115:20-117:8.) Both Dr. VanDenburgh and Dr. Woodward received this memo and three others dated January, March, and April 2000, all of which showed eyelash growth. (PTX 171; PTX 184A; PTX 185A; Tr. 11/5/12 at 210:15-24, 212:5-213:10; Tr. 11/6/12 at 117:23-121:25.) This evidence supports and corroborates Dr. Woodward's testimony of a mid-2000 invention date.[12] Thus, the Brandt references are not prior art under 35 U.S.C. § 102(a) and could not have anticipated the '404 Patent's claims.[13]

[12] Accordingly, Defendants' motion pursuant to Federal Rule of Civil Procedure 52(c), (Tr. 11/8/12 at 31:6-35:3; Doc. 178), is denied.

[13] In fact, none of these references can claim a date earlier than March 2001. The October 23 presentation teaches only that a compound named AGN 192024, when applied to treat glaucoma, has an adverse event of eyelash growth in more than 5% of patients. (DTX 6.) Defendants presented no credible evidence that a person of ordinary skill in the art would have known that AGN 192024 was bimatoprost before FDA approval of Lumigan® on March 16, 2001. (*See* Tr. 11/9/12 at 97:11-12 ("The structure had been kept pretty much under wraps by Allergan . . . ."); Tr. 11/20/12 at 22:19-24:2 (calling into question authenticity, relevance, and public knowledge

Even if the inventors are not entitled to a conception date earlier than the February 4, 2002, effective filing date, none of the Brandt references alone anticipates the '404 Patent. *See, e.g., Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) ("[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation."). The October 23 presentation discloses no method of application; and even assuming a person of ordinary skill in the art knew that this glaucoma medication was to be applied by eye drop, the Court has already determined that hair growth is not inherent in such an application.

The same is true of the remaining Brandt references and the '819 Patent. All of the Brandt references disclose the adverse side effect of eyelash growth when the unidentified compound is used to treat glaucoma. (*See* DTX 710, 695, 720, 735, 113.) However, none of them teaches that an effective amount of bimatoprost to stimulate hair growth is applied when bimatoprost is used to treat glaucoma or that eyelash growth necessarily results from the application of bimatoprost to treat glaucoma. In fact, none of the references disclose more than a 48.4% incidence of eyelash growth as a side effect of bimatoprost applied through an eye drop to treat glaucoma. (DTX 710 at -001; DTX 720 at -002; DTX 113 at -006, -010; DTX 735 at -006); *see Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995) (declining to find inherency even though defendant's chemists reproduced prior art method "thirteen times and each time they made [the claimed] crystals," because different crystals were produced twice by

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of DTX 17).) Similarly, the October 23 press release, the March 2 presentation, and the March 2 press release refer to the compound as Lumigan®, which was not associated with bimatoprost until Lumigan® was approved. (DTX 695, DTX 710, DTX 720; Tr. 11/9/12 at 41:17-20; Tr. 11/13/12 at 156:23-157:4, 164:17-165:17.)

patentees' chemists). Likewise, as stated above, the '819 Patent does not inherently teach the application of an effective amount of bimatoprost to stimulate eyelash growth.

Finally, Defendants contend that the '029 Patent anticipates the '404 Patent because it is a small genus of which a person of ordinary skill in the art would "at once envisage" the species—the '404 Patent. *See In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962). "It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus. . . . On the other hand, a very small genus can be a disclosure of each species within the genus." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

The '029 Patent is not a genus so small that it discloses the '404 Patent's claims. The '029 Patent expressly depicts the structures of approximately one hundred compounds, yet it does not expressly depict or describe the structure of bimatoprost. (PTX 2 at 9:1-22:19, 29:39-40:44; Tr. 11/19/12 at 173:10-12.) Dr. Macdonald testified that the number of compounds identified by the '029 Patent are so numerous that a person of skill in the art would not be able to visualize them. (Tr. 11/19/12 at 172:19-173:9.) In fact, the Markush structure of the '029 Patent includes four main variables, each of which can be selected from a group including several general options, resulting in several thousand compounds. (PTX 2 at 7:13-8:21; Tr. 11/9/12 at 93:19-94:4; Tr. 11/19/12 at 171:16-172:18.) Dr. Macdonald further testified that one of ordinary skill in the art would not understand the '029 Patent to state a preference for bimatoprost because it does not indicate that an amide is a preferred structure. (Tr. 11/19/12 at 174:1-175:4, 175:22-176:5.) The mere fact that it is possible to build bimatoprost using the '029 Patent, as illustrated by Dr. Sherman, shows not that the '029 Patent is anticipatory, but that it is the genus to the '404 Patent's species. (*See* Tr. 11/9/12 at 91:10-94:10.) The '029 Patent does not disclose the '404

Patent claims "such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys.*, 212 F.3d at 1282.

B. Obviousness

Under 35 U.S.C. § 103(a), a patent is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." § 103(a). Generally, to show that a patent is invalid as obvious, the challenger must "demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 1361 (Fed. Cir. 2007)).

To determine whether a patent is obvious, courts must make four factual inquiries, examining

> (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the field of the invention; and (4) objective considerations such as commercial success, long felt but unsolved need, and the failure of others.

Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc., 699 F.3d 1340, 1347 (Fed. Cir. 2012) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

1. The '029 Patent

Defendants contend that the Johnstone PCT and the '819 Patent render the '029 Patent obvious. Specifically, Defendants argue that the Johnstone PCT's teaching that 17-phenyl $PGF_{2\alpha}$

glaucoma drugs grow hair would have motivated a person of skill in the art[14] to test the '819 Patent's glaucoma drugs for effectiveness in hair growth.

The Johnstone PCT and the '819 Patent are too limited and too different from the '029 claims to make obvious the hair growth properties of the '029 compounds to a person of ordinary skill in the art. The Johnstone PCT includes compounds that have carboxylic acids or esters at the C-1 positions; it does not disclose that saturated prostaglandin compounds having a C-1 amide group, like those in the '029 Patent, can grow hair. (Tr. 11/9/12 at 210:18-211:10; Tr. 11/19/12 at 149:23-150:25.) Although the '819 Patent discloses bimatoprost as a glaucoma drug, it does not supply the missing link that Defendants seek. A person of ordinary skill in the art would not have been motivated to use bimatoprost to grow hair, as it was understood to be pharmacologically different than other prostaglandin analogs. (*See, e.g.*, Tr. 11/5/12 at 210:7-14.) C-1 acids were thought to be required for activity at the FP receptor, and bimatoprost has an amide rather than an acid at the C-1 position. (Tr. 11/19/12 at 7:11-8:2, 197:7-16, 198:20-199:8, 202:6-12.) Bimatoprost was thought to exert activity on a receptor other than the FP receptor, and therefore was distinguishable from the Johnstone compounds. (DTX 738 at 9:5-13:55; PTX 691 at 2; Tr. 11/19/12 at 11:5-13:9.)

These pharmacological differences are especially significant in the hair growth field. The evidence showed that hair growth is and was unpredictable and mysterious. (Tr. 11/19/12 at 91:10-14.) There are only three FDA-approved drugs for hair growth including Latisse®. (*Id.* at 83:16-24.) At the time of the invention, $PGF_{2\alpha}$ analogs were known to have different hair

[14] The evidence showed and the Court finds that a person of ordinary skill in the art would have a master's or doctorate degree in medicinal chemistry, chemistry, biochemistry, pharmacology, or biology, or a related field, with two or more years of experience in designing, developing and/or investigating compounds for possible pharmaceutical use or their pharmacology. (Tr. 11/7/12 at 123:10-19.)

growth effects despite their similar effects of reducing IOP. (*Id.* at 91:20-97:22.) As illustrated by the Johnstone PCT, latanoprost was reported to promote hair growth. (DTX 499.) Tromethamine salt, on the other hand, was shown to inhibit the regrowth of hair in mice. (Tr. 11/19/12 at 93:6-95:13; PTX 486.) The label for the glaucoma drug Rescula® includes a warning that 10-14% of patients had increased length of eyelashes, 7% had decreased length of eyelashes, and 80% showed no response whatsoever. (Tr. 11/19/12 at 96:6-97:5; PTX 443.) Thus, a person of skill in the art would not have reason to use bimatoprost as a topical hair growth agent based on bimatoprost's identity as a prostaglandin analog alone.

The objective considerations also weigh against obviousness. In light of the pharmacological differences between bimatoprost and other prostaglandin analogs, hair growth was an unexpected result. (Tr. 11/6/12 at 48:20-49:16, 106:7-110:9; PTX 579 at -405; PTX 536 at -527.) Additionally, Latisse® has been a commercial success. While its sales did not meet initial projections, the sales numbers have been impressive for a product marketed for cosmetic use during a recession and have increased in the years since the product was launched. (PTX 669 at -664-65; Tr. 11/13/12 at 210:11-211:7.) The product is the fourth largest medical aesthetic product on the market and has a 94% patient satisfaction rate.[15] (PTX 465 at -087; Tr. 11/13/12 at 209:4-19, 213:13-215:6.) Additionally, Latisse® is one of only three approved hair-growth drugs, and it is the only one to grow eyelashes; not even latanoprost, the subject of the Johnstone PCT, has been approved and marketed to grow eyelashes.

[15] The Defendants' expert on commercial success was thoroughly and persuasively impeached, and the Court finds his testimony was not credible.

2. The ‘404 Patent

Defendants contend that the ‘404 Patent is rendered obvious by the Johnstone PCT and the ‘819 Patent combined. The Johnstone PCT and the ‘819 Patent do not render obvious the claims of the ‘404 Patent for the same reasons they do not render the ‘029 Patent obvious.

Defendants further contend that the ‘404 Patent is rendered obvious by the Brandt references alone and in combination with the Johnstone PCT. The Brandt references could not have been combined to achieve bimatoprost as a hair growth agent because they are not prior art. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1480 (Fed. Cir. 1997) (“The obviousness of a patent claim is determined ‘at the time the invention was made.’” (quoting 35 U.S.C. § 103)). The Johnstone PCT alone did not make the ‘404 Claims obvious because, as stated above, the compounds were too pharmacologically different to motivate a person skilled in the art to treat them the same way. Thus, the prior art did not render the ‘404 Patent claims obvious.

C. Section 112 Defenses

Under 35 U.S.C. § 112, a patent specification must “contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same.” Three requirements are encompassed by § 112, two of which Defendants raise as defenses to infringement: 1) written description, and 2) enablement. *See Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 921 (Fed. Cir. 2004) (listing three requirements).

1. Written Description

A patent applicant must “convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.” *Vas-Cath Inc.v.*

Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (emphasis omitted). "It is not necessary that the application describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that [the inventors] invented processes including those limitations." *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976) (citation omitted). The written description must actually or inherently disclose all the claim elements. *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-07 (Fed. Cir. 2008). In disclosing a large genus of compounds, the inventor must make "blazemarks as to what compounds, other than those disclosed as preferred, might be of special interest." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996).

Defendants contend that the '029 Patent fails to meet the written description requirement because the specification does not support the provisos in claims 1, 18, and 20. The provisos state that "when the bond at the C2-C3 position is a single bond, the bond at the C5-C6 position is a double bond, R^1 is a C(O)OR^3 and R^3 is a monovalent hydrocarbon group or substituted monovalent hydrocarbon group," then R^2 is not a hydrogen pursuant to claim 1, (PTX 2 at 61:43-47); X must be "selected from the group consisting of –C=C-, -CH=C=CH-, -CH=CH- and –CH=N-" pursuant to claim 18, (*id.* at 64:8-14); and Z must be "selected from the group consisting of a heterocyclic group, a substituted heterocyclic group and a substituted heteroaromatic group" pursuant to claim 20. (*Id.* at 66:9-15.)

The provisos operate to exclude the Johnstone compounds, which are not selective for the FP receptor. (Tr. 11/19/12 at 145:14-149:16, 165:8-22; *see also* Tr. 11/6/12 at 212:17-213:11.) The specification supports the provisos. The summary of the invention explains:

> The methods comprise administering the compositions comprising specific prostaglandin analogs that interact strongly with hair-selective receptors, such as the FP receptor. The choice of prostaglandin analog is important because the

> prostaglandin analogs must selectively activate the FP receptor and not activate any other receptors that would negate the effect of activating the FP receptor.

(PTX 2 at 3:14-20; *see* Tr. 11/19/12 at 165:8-166:2.) The Patent defines "selective" as "having a binding or activation preference for a specific receptor over other receptors which can be quantitated based upon receptor binding or activation assays." (PTX 2 at 5:53-55; Tr. 11/19/12 at 166:6-14.) The patent also specifically describes latanoprost in Comparative Example 1, noting that it is nonselective and that it "activates the EP_1 receptor, which which [sic] results in the side effect of causing pain." (PTX 2 at 56:22-49; Tr. 11/19/12 at 167:11-25.)

"Negative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1351 (Fed. Cir. 2012). The written description here is effectively indistinguishable from that approved by the Federal Circuit in *Santarus*. There, the court determined that a proviso excluding the compound sucralfate was adequately supported by specification language indicating that the claimed composition was "advantageous" as compared to sucralfate, even where sucralfate was positively recited in the specification. *Santarus*, 694 F.3d at 1350-51.

Likewise, here, the '029 Patent specification describes the Johnstone compounds as non-selective compounds that could be suitable as hair growth stimulants, (PTX 2 at 47:8-21, 47:53-57); however, the specification gives their non-selectivity as a clear reason to exclude them. "Such written description support need not rise to the level of disclaimer." *Santarus*, 694 F.3d at 1351. Like the claim limitation in *Santarus*, the '029 provisos are "adequately supported by statements in the specification expressly listing the disadvantages" of the Johnstone compounds generally and latanoprost specifically. *See id.*

2. Enablement

Defendants contend that both patents are invalid for lack of enablement. A patent is enabling if the specification "provide[s] sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation." *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1337 (Fed. Cir. 2005). Some experimentation does not preclude a finding of enablement; however, the experimentation must not be undue. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). To determine whether one skilled in the art could make and use the invention without undue experimentation, courts consider a variety of factors, including

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. at 737.

The '029 Patent is enabled because it provides sufficient information for a person of skill in the art to make and use the compounds without undue experimentation. Although the hair growth field is unpredictable, the patent provides sufficient teaching to one skilled in the art. First, the patent teaches how to chemically synthesize the prostaglandin F analogs claimed in the patent. (PTX 2 at 22:22-29:37, 41:32-43:67.) The patent also describes a telogen conversion assay used to determine if a compound could treat hair loss, (PTX 2 at 54:58-55:65; Tr. 11/6/12 at 206:13-19; Tr. 11/19/12 at 250:24-253:2), and a radioligand binding assay to determine if a compound is FP-selective. (PTX 2 at 54:15-57; Tr. 11/19/12 at 168:17-169:22.) Plaintiffs provided evidence that such assays would be routine for persons of ordinary skill in the art, (Tr. 11/19/12 at 6:6-12, 170:16-18), and Defendants provided no contradictory evidence to show that

such experimentation would be undue. Dr. Macdonald's testimony does not establish that the experimentation needed to identify bimatoprost as an effective compound to grow hair would be undue; rather, he simply acknowledged the facts that the '029 Patent covers many compounds and that some experimentation would be necessary to determine which of them effectively grew hair. (*Id.* at 242:13-21, 248:15-18.) Dr. Macdonald specifically testified that such experimentation would not be extensive. (*Id.* at 248:15-18.) Finally, the '029 Patent teaches use of the compounds, describing compositions of the invention, made up of the claimed compound and a carrier suitable for administration to a mammal, (PTX 2 at 44:36-53:26), and the mode of application of the invention, including information on dosage and topical administration. (*Id.* at 53:28-54:8.)

In pre-trial submissions, Defendants did not mention any contention that the '404 Patent was invalid for lack of enablement. (Doc. 129; Doc. 158.) Nor was this contention raised clearly at trial. Therefore, this argument has been waived. *See, e.g.*, *Alza Corp. v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 622 (D. Del 2009). Even assuming the argument has not been waived, it fails on the merits because it is inconsistent with the Court's claim construction. (Doc. 180.) Defendants specifically contend that the '404 Patent does not support the claim that bimatoprost stimulates hair growth by "convert[ing] vellus or intermediate hair to growth as terminal hair, decreas[ing] the number of telogen hairs, prevent[ing] atrophy of hair follicles, or increas[ing] the number of hairs." (*See* Doc. 190 at 34-35 (internal quotation marks and alterations omitted).) Yet the Court's claim construction defines "a method of stimulating hair growth" with a list of alternatives, any of which would satisfy the requirements of claim 14. Thus, the Patent need only teach a person of skill in the art to make and use bimatoprost to stimulate hair growth in one of the listed ways. Defendants presented no evidence that the '404

Patent does not teach one of skill in the art to use bimatoprost to increase the length and thickness of hair, along with several of the other alternatives, and indeed the evidence is to the contrary. Because the '404 Patent does teach such use, it does not fail for lack of enablement.

IV. Conclusion

For the foregoing reasons, the Court concludes that Plaintiffs have met their burden to prove, by a preponderance of the evidence, that Defendants' ANDA products infringe claims 1, 8, 14, 18, and 20 of the '029 Patent and claim 14 of the '404 Patent under the Court's construction. Defendants have not proven, by clear and convincing evidence, that the '029 and '404 Patents are invalid.

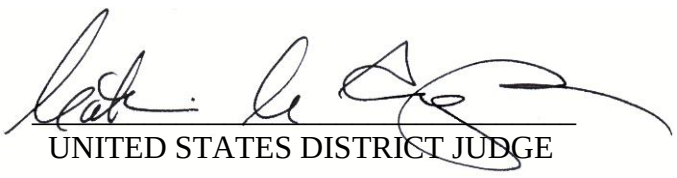
If a court finds a patent infringing under 35 U.S.C. § 271(e)(2)(A), it "shall order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." 35 U.S.C. § 271(e)(4)(A). The Court has found such an infringement.

It is therefore **ORDERED** that:

1. Defendants' Rule 52(c) motion for judgment on partial findings is **DENIED**.
2. The effective date of approval of Defendants' ANDA products shall be a date which is not earlier than the later of the expiration dates of the '029 and '404 Patents.

As time permits, the Court will enter a judgment in favor of Plaintiffs and against Defendants consistent with this Memorandum Opinion and Order.

This the 24th day of January, 2013.



UNITED STATES DISTRICT JUDGE